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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,024	09/12/2005	Rene Bernards	BJS-620-378	8133

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,024	BERNARDS ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-10 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-10 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-4-08.

Claims 5-10 and 13 are pending in the instant application.

Information Disclosure Statement

The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

Response to Arguments and Amendments

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 1-4-08 and for the reasons set forth below.

Applicant's arguments filed 4-4-08 have been fully considered but they are not persuasive. Applicant argues that adequate written description has been provided for the genus comprising *promoters that comprise a target site recognized by HIF*, and for the genus comprising *conditions whereby VDU1 is capable of stabilizing HIF-alpha in the absence of a modulator* on pages 19 and 41 of the instant specification.

Contrary to Applicant's assertions, page 19 merely discloses the well known fact that the HIF pathway is at a low level of activation under normoxic conditions, and that the HIF pathway is at a high level of activity under hypoxic conditions. The disclosure of these well known facts, however, does not satisfy the requirement for adequate written description of the genus comprising *conditions* where VDU1 is capable of stabilizing HIF-alpha in the absence of any modulators. The text provided on page 19 is an invitation to experiment to determine what the conditions might be that allow VDU1 to stabilize HIF-alpha, as opposed to informing one of skill in the art as to what those

conditions are that regulate or modulate the ability of VDU to deubiquitinate its substrates. In order to successfully screen for the presence of modulators, the conditions for such screening must first be established.

Page 41 lists commercially available reporter proteins (such as GFP or SEAP) that are optionally subcloned downstream of NF-kappa-beta. A representative number of species have not been described for the genus comprising *promoters having target sites recognized by HIF*, and the disclosure of commercially available reporter proteins does not fulfill the requirements for concisely describing the members of the genus of target sites that exist on promoters that are recognized by HIF.

For these reasons, the instant rejection for lacking adequate written description is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (BBRC, Vol. 294, pages 700-709, 2002) and Li et al (J.Biol. Chem.., Vol. 277, No. 7, pages 4656-4662, 2002), the combination further in view of Jones et al FASEB J., Vol. 16, pages 264-266, 2002) for the reasons of record set forth in the Office action mailed 1-4-08 and for the reasons set forth below.

Applicant's arguments filed 4-4-08 have been fully considered but they are not persuasive. Applicant argues that, prior to the present discovery, no target for deubiquitination by VDU1 had been identified and no physiological role for deubiquitination had been demonstrated. Applicant also argues that no art of record teaches that HIF-alpha could be deubiquitinated by VDU, and that deubiquitination would not lead to the degradation of HIF. Rather, according to Applicant, deubiquitination would stabilize HIF-alpha and prevent its degradation by the proteasome. Applicant also argues that the association of high HIF-alpha levels with angiogenesis would not have suggested that HIF-alpha is a target for deubiquitination and that modulation of HIF stability would not have been presumed to be due to deubiquitination.

Applicant is correct that the prior art taught a correlation between loss of ubiquitination due to VHL mutations (and hence VHL inactivation) in various forms of cancer: “Recently, Ohh et al has demonstrated that pVHL binds directly to HIF through

its beta-domain and targets HIF for ubiquitination. Mutations in either pVHL alpha or beta-domain may cause an overaccumulation of HIF in affected cells, which helps explain why highly vascularized tumors develop in VHL disease…" (Li et al, J.Biol. Chem.., Vol. 277, No. 7, pages 4656-4662, 2002, at 4662).

It is further noted that Li pointed out the relationship between HIF ubiquitination and the accumulation of HIF-1-alpha: "Recent studies revealed that hypoxia-inducible factor, HIF-1-alpha, is a substrate of VCB-CUL-2 E3 ligase for ubiquitination and degradation at normoxia via physical interaction with the core of the oxygen-dependent degradation domain." (see Li et al, JBC, Vol. 277, No. 7, 2002 at page 4656) (references omitted). And it was well known at the time of the instant invention that VHL gene mutations lead to its inactivation in various forms of cancer: "VHL gene mutations can be detected in 100% of patients who carry a clinical diagnosis of VHL disease." (Id. at 4656). Without functional pVHL, HIF1 can be accumulated in cells resulting in overexpression of HIF1 target genes…" (Id. at 4656).

Applicant argues that Li teaches only that VHL binds to VDU1 and ubiquitinates it for degradation, and that no suggestion that HIF-alpha is involved in this process. There is no mention of deubiquitination of HIF-alpha in the cited reference, according to Applicant, and the deubiquitinating activity of VDU1 was demonstrated using an artificial substrate.

Contrary to Applicant's assertions, Li taught that VDU had deubiquitinating activity: "Enzymatic function studies demonstrate its deubiquitinating activity." (Id. at 4657). Li also addressed the significance of deubiquitinating enzymes in regulating

protein stability in the cell: "[T]he ubiquitination process is also involved with another class of enzymes, deubiquitinating enzymes... Possible functions of deubiquitinating enzymes include…rescuing proteins from degradation by removing ubiquitin from protein substrates, therefore competing or counteracting with the ubiquitin-conjugating system." (Id. at 4661).

So, contrary to Applicant's assertions, one of skill in the art would have logically investigated whether changes in the ubiquitination of HIF would modulate its stability, and hence its activity. As a matter of fact, Li explicitly asks that question: "Can VDU1 and VDU2 deubiquitinate the ubiquitinated downstream targets of pVHL-E3 ligase, such as HIF-1-alpha…? (Li et al., BBRC, Vol. 294, pages 700-709, 2002, at 708).

For these reasons, the instant invention, drawn to methods to screen for modulators of VDU1 stabilization of HIF-α or the state of ubiquitination of HIF-α comprising contacting a test system in a cell with a candidate modulator, which test system comprises VDU1, HIF-α and further comprises VHL and optionally testing under hypoxic and normoxic conditions, would have been obvious to one of ordinary skill in the art at the time the instant invention was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
6-24-08
/Jane Zara/
Primary Examiner, Art Unit 1635